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AUTHORITY

USAMRMC ltr, 19 Sep 2002

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AD______________

Award Number: DAMD17-00-1-0456

TITLE: Evaluating the Effectiveness of Screening Mammography in Women from Older and Disadvantaged Populations

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REPORT DATE: September 2001

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Kath Moore 1/4/02

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)

2. REPORT DATE
September 2001

3. REPORT TYPE AND DATES COVERED
Annual Summary (1 Apr 00 - 31 Aug 01)

4. TITLE AND SUBTITLE
Evaluating the Effectiveness of Screening Mammography in Women from Older and Disadvantaged Populations

5. FUNDING NUMBERS
DAMD17-00-1-0456

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (proprietary information, Sep 01). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

12b. DISTRIBUTION CODE

13. Abstract
The objective of this study was to investigate the relationship between prior screening mammography use and cancer stage/tumor size at diagnosis for women aged 67 and older diagnosed with primary breast cancer in 1994, 1995 or 1996 and having a linked SEER-Medicare record. Of interest was the effectiveness of screening mammography in women aged 75 and older compared to women aged 67-74, and the effectiveness of screening mammography in non-Hispanic whites compared to African Americans and Hispanics. Women 75 and older were significantly more likely to be diagnosed with non-local disease (stage IIA or higher) and have larger tumors than women 67 to 74 years of age. However among regular users of mammography, both women 65-74 years old and 75 years and older were diagnosed with the same size tumor and same percent non-local stage tumors. These results were similar after adjusting for sociodemographic and comorbidity information. African American and Hispanic women were significantly more likely to be diagnosed with non-local stage disease and larger tumors than white women. However when women were regular users of mammography the difference was not significant. Regular use of screening mammography eliminates differences in tumor size and stage of cancer at diagnosis observed in older women and minority groups.

14. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)
breast cancer detection, screening mammography, population based, Outcomes analysis, Medicare-Tumor Registry linked database

15. NUMBER OF PAGES
46

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction:

Screening mammography has been shown to be an efficacious method of reducing breast cancer mortality in a number of randomized controlled trials. A survival benefit has been demonstrated in women up to age 69; however, evidence to support reduced mortality in women 70-74 was inconclusive, and no trails have included women 75 and older. This paucity of information has led to a lack of consensus regarding recommendations for mammography in women age 70 and up. Therefore the objective of this study was to investigate the relationship between prior screening mammography use and cancer stage or tumor size at diagnosis for women aged 67 and older diagnosed with primary breast cancer in 1994, 1995 or 1996 and having a linked Medicare record. The main questions were whether the effectiveness of screening mammography is similar in women aged 75 and older compared to women aged 67-74, and if the effectiveness of screening mammography is similar in non-Hispanic whites, African Americans and Hispanics. The study utilized the linked Medicare - Tumor Registry Database, which contains population-based data on breast cancer cases from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Each subject's Medicare claims were reviewed to evaluate her mammography use for the 24 months prior to her breast cancer diagnosis. A screening mammography algorithm was used to determine whether any mammogram found was screening or diagnostic. Screening mammogram use was evaluated to determine its impact on size or stage of cancer at diagnosis.

Body:

Task One: To identify the study population from the linked SEER-Medicare database and construct an analytic file with the study variables.

A) Identify the women 67 and older who have a diagnosis of breast cancer in 1994, 1995 and 1996 and have a linked SEER-Medicare record

B) Construct the analytic file with study variables

<u>Sample Selection</u>

Eligible women for the study were 67 years of age and older with an incident case of primary breast cancer diagnosed between January 1, 1994 and December 31, 1996 and reported to the SEER registry. In order to assess the effect of regular mammography use on size and stage of breast cancer at diagnosis, two years of claims data prior to diagnosis had to be available. Therefore women who were enrolled in a health maintenance organization or did not have Medicare Parts A&B for any time for the two years prior to diagnosis were excluded, as HMOs do not reliably report claims to Medicare and women missing Parts A & B coverage at any time will have no claims for that missing time period.

The study sample was selected using the following steps (Figure 1). From the original PEDSEF file for that year all persons with an incident breast cancer were chosen. Then the small percentage of men with breast cancer was eliminated. For the women, their Medicare coverage for the period of two calendar years prior to year of diagnosis was assessed and those women with 12 complete months of Part A and B coverage for each year and no HMO enrollment were retained. Women without full coverage or with HMOs were dropped to ensure that there were two years of Medicare claims available prior to the present breast cancer diagnosis.

Figure 1 – Selection of Study sample for the years 1994, 1995, and 1996

	Original sample size from PEDSF file (1994) N=13,124	Original sample size from PEDSF file (1995) N=13,204	Original sample size from PEDSF file (1996) N=12,314
Diagnosis breast cancer 1/1-12/31	N=13,124	N=13,204	N=12,314
age >=65 in year of diagnosis	N=10,237	N=10,622	N=10,257
Had full coverage of Part A &Part B, no HMO at year of diagnosis	N=7317	N=7369	N=6978
Had full coverage of Part A &Part B, no HMO for year prior to diagnosis	N=6894	N=6927	N=6569
Had full coverage of Part A &Part B, no HMO two years prior to diagnosis	N=6460	N=6523	N=6194
Were 67 or older in year of diagnosis	N=6366	N=6478	N=6164

To further guarantee a sample of Medicare age-eligible women with two prior years of claims, women who were younger than age 67 were dropped. This was a small number for all years as most women younger than age 67 were already eliminated due to not having two full years of coverage. The cohorts from each year were combined to constitute a sample of 19008 women. Women with American Indian, Other or Unknown race, about 1.5% of the sample, were removed before analysis. After preliminary analysis the group labeled Asian/Pacific Islander consisting of Chinese, Japanese, Filipino and Hawaiian women was also excluded for lack of power. This group made up about 2.3% of the original sample.

We then created two samples for analysis. From the original sample we first eliminated women who had no data available on size of tumor such as Paget's disease or women with missing tumor size were excluded (n=2322) about 13% of the sample, which left a final sample of 15967 women. Going back to the original sample again, we eliminated those women with no data available on AJCC stage of tumor. This resulted in a sample of 17009 women.

Because a much larger number of women were missing size data, we performed additional checks to determine how they differed from the sample with size information. Of the 2322 women that were excluded from the sample based on missing size information, 1095 (about 47%) had an unknown AJCC stage. Of the remaining women without tumor size data about 40% were stage 0 (in situ) cancers (Table 1). Both of these percentages were much higher than in the remaining sample with size information. We also compared the women missing tumor size data to those with it by race and age. There were some slight differences depending on race/ethnicity. Of whites 12% were missing size of tumor data, 18% of blacks were missing size information, and 10% of Hispanics were missing information on size of tumor. There were very few differences by age at diagnosis (1-2%). There were also few differences by previous use of screening mammography – 14% of non-users lacked tumor size information, 12% of single users and 12% of regular users were missing size information.

Table 1. Presence or Absence of tumor size information by AJCC stage at diagnosis (row percents)

Tumor size info	0	I	2A	2B	2, NOS	3A	3B	4	Un-known
YES	1245	8172	3731	1375	0	454	424	381	185
	8%	51%	23%	9%	0%	3%	3%	2%	1%
NO	797	36	4	3	129	12	72	174	1095
	34%	2%	0.25%	0.25%	5.5%	0.5%	3%	7.5%	47%

Measures

Outcome Variables

The main outcome variables were tumor size at diagnosis and AJCC stage at diagnosis. Both variables were found in the Patient Entitlement and Diagnosis Summary File (PEDSF), as described above. Data were available on tumor size for 15,967 subjects and on stage for 17,009 subjects.

<u>Tumor Size</u>

Size of tumor was chosen as the outcome variable because it is a good independent predictor of survival and is less subject to the biases inherent in the staging process (Samet JM et al. 1990). Tumor size as a continuous variable has been found to be an independent predictor of survival (Carter CL et al. 1989). Tumor size has a sizable effect on 5-year survival, which decreases with larger tumor size even if there is no lymph node involvement (Carter CL et al. 1989). Additionally, as the number of lymph nodes involved increases, survival decreases even if the tumor is small, as node involvement may serve as a marker of a tumor's aggressiveness in spreading (Carter CL et al. 1989).

Size of tumor was ascertained from the PEDSF file. Size is coded using part of the 10-digit Extent of Disease (EOD) Coding system. In the EOD coding system, the first three digits indicate size of the primary tumor in millimeters, the next 2 describing extension, followed by 1 digit for lymph nodes, 2 digits for number of positive regional lymph nodes, and 2 digits for number of regional lymph nodes examined. We used the first three digits of the EOD number that describe tumor size. According to the EOD documentation the exact size of the primary tumor is recorded in millimeters. The largest dimension or diameter of a tumor is always recorded. If the tumor is mixed in situ and invasive, only the invasive portion is recorded. If the tumor is characterized as in situ, then the actual size of the tumor is recorded. Pathologic size is not to be recorded if a patient had pretreatment with neoadjuvent chemotherapy, radiation therapy, hormonal therapy, or immunotherapy (SEER EOD-88 3rd edition – January 1998).

There are some special coding rules specific for breast cancer tumors – '000' is used when no mass or tumor is found but the tumor has metastasized, '002' is a non-palpable tumor discovered or diagnosed mammographically only, Paget's disease of the nipple with no underlying tumor is coded as '997', and '998' is used to indicate inflammatory carcinoma or a diffuse, widespread tumor ¾ or more of the breast.

In preparing the size variable for analysis women with codes of '000', '002', and '997' were coded as missing along with the women who had no tumor size recorded. Additionally, 12 women who had a '998' code - Inflammatory but an AJCC stage of less than IIIB were excluded as AJCC rules dictate that women with inflammatory cancer be Stage IIIB or higher. We also checked to see if the larger tumor, those coded 5 centimeters or more were Stage IIB or higher, another AJC rule. Size was treated as a continuous outcome variable, measured in millimeters. All tumors greater than 100 millimeters (n=59) were grouped together with inflammatory cancers (n=113) into a category of 110 millimeters. We felt that most women with these sizes of tumor or inflammatory cancer represented a group of women with large and/or aggressive tumors. There were 2322 women in the original sample who were missing information on size of tumor at diagnosis, leaving 15967 available for analysis.

<u>AJCC Stage at diagnosis</u>

American Joint Committee on Cancer staging, AJCC Stage at diagnosis, was chosen as the outcome variable for stage. Stage was a categorical variable with a woman assigned to one category based on size of tumor, number of nodes involved, and extent of disease. There are seven stages of breast cancer. I, IIA, IIB, IINOS, IIIA, IIIB, and IV. Tumors could also be classified as in situ. The majority of analyses had women classified as either local (in situ or Stage I) or non-local (Stage II and higher) stage. After excluding women without stage information there was a sample consisting of 17009 women, of whom 2042 (12%) were classified with in situ tumors.

Mammography

Operational Definitions of Screening Mammograms

We were primarily interested in the effect of mammography on size and stage of cancer at diagnosis and in how screening mammography affected the relationship of age and race to size and stage at diagnosis. Previous investigations of mammography use with the Medicare data have utilized three different approaches to identify claims for screening mammograms: 1) Any mammogram claim – CPT codes 76090 (mammography, unilateral), 76091 (mammography, bilateral), 76092 (screening mammography, bilateral); 2) Any bilateral mammogram claim – CPT codes 76091, 76092 and 3) Any screening mammogram claim – CPT code 76092 population (MMWR – Anonymous 1995, Blustein J et al. 1995, Burns RB et al. 1996, Burns RB et al. 1996, Ives DG et al. 1996, Preston JA et al. 1997, Blustein J & Weiss LJ 1998, May DS & Trontell AE 1998, Parker JD et al. 1998, Welch HG & Fisher ES 1998, Parker JD et al. 1999, Smith-Bindman R et al. 2000).

In this study, a fourth approach was used that identified mammograms provided to asymptomatic women by examining their history of mammography use and diagnoses prior to the mammogram: any bilateral mammogram claim in the physician claims file with a) no evidence in the woman's physician claims files of a previous mammogram performed within the 11 months and prior to (but not including) the mammogram date and b) no evidence in any of her claims files of a previous breast mass/breast cancer diagnosis in the two years prior to (but not including) the mammogram date. Bilateral mammogram claims with a CPT code of 76092 must also have a diagnosis code of v16.3, v10.3, v72.5 or v15.89 in any of the diagnosis fields.

Measures of Mammography Use

Another issue in assessing prior mammography use is how to classify women as non-users and users of screening mammography. McCarthy et al. published studies in 1998 and 2000 assessing how prior mammography use affected breast cancer at diagnosis. Because the screening code (CPT 76092) was not yet in use for the years of their data they used the bilateral mammography code to classify women into non-users, peridiagnostic users, regular users, and uncertain users of mammography. Non-users had no prior bilateral mammography, peridiagnostic users only had mammograms within three months of diagnosis, and regular users had 2 or more mammograms at least 10 months apart. The uncertain category appears to include women with a single bilateral mammogram not within three months of diagnosis and women with more than one mammography not 10 months apart. In McCarthy's analyses the uncertain women were thrown out of the analysis in addition to women with peridiagnostic use. The peridiagnostic women's mammograms had to be assumed to be diagnositic because of their proximity to the diagnosis date. A better way of determining screening from diagnostic would enable many of the women lost in the peridiagnostic group to be used in our analysis.

We modified the classification criteria to include a newer definition of screening mammograms. We used our screening mammogram algorithm to test any bilateral mammogram claim. Women were then classified into one of three categories based on their prior screening mammography use. Nonusers had no screening mammography in the 24 months prior to diagnosis, but could have undergone diagnostic mammograms. Single-users had at least 1 or more screening mammograms in the 24 months prior to diagnosis but none were 10 months apart. Regular-users had 2 or more screening mammograms at least 10 months apart in the 24 months prior to diagnosis. In both the size and stage analysis groups 34% of women were nonusers, 51% single users, and 15% regular users.

Other Variables

Sociodemographic variables of interest were obtained from the PEDSF file. Age at diagnosis was dichotomized into two groups (67-74, 75 or older). Race or ethnicity was determined to be Caucasian, African American, Caucasian Hispanic or other/unknown racial/ethnic groups. Other/unknown women were excluded from analysis. Marital status at diagnosis was also dichotomized into currently married (married) or not currently married (widowed, divorced, separated, single). SEER area of residence was determined by stripping the first 2 numbers from the SEER identifier and matching them up with the code for each region. Geographic information on socioeconomic (SES) factors included in the

PEDSF file was used to approximate SES. The information for these variables was estimated according to a subject's age group and race/ethnicity by estimating medians and proportions from US Census Bureau tables containing values for race and age categories. We chose to use median income data from area of residence as a proxy for SES, as these have been shown to be valid proxies for individual SES (Krieger N 1992). Income was also dichotomized into categories of equal or greater than $25,000 or less than $25,000. Comorbidity was measured using an adaptation of the Charlson (1987) index that was developed by Klabunde CM et al. (2001) for Medicare claims data. This adaptation is based on using comorbidity information from the ICD-9-CM diagnosis codes (and one procedure code) in both inpatient and physician claims, with a date of service in the year prior to the month of the cancer diagnosis. The index is derived with inpatient and physician weights (coefficients from the Cox regression model) corresponding to the individual conditions in the original Charlson index translated to ICD-9 conditions by Deyo et al. (1992). Consistent with Klablunde CM et al. (2001), we first excluded all conditions occurring in the same month of the cancer diagnosis and then excluded other solid tumors, leukemia and lymphomas. Since these conditions are often confounded with breast cancer. We also excluded ICD-9-CM diagnosis codes from Part B clinical laboratory, diagnostic imaging and durable medical equipment claims. If a code appeared only once in the physician claims for the year and an identical code was not present in the Part A files then it was excluded. If a code appeared more than once in a 30 day period in the physician claims but never again in Part A or B then it was excluded. We searched each subject's inpatient and physician claims for evidence of the conditions using Klabunde CM et al.'s criteria and added the weights corresponding to each condition that was present. If the condition was present in both the inpatient and the physician claims we used the inpatient weight. The exponentiated sum of the weights for each subject was her measure of comorbidity.

Task Two: To generate descriptive tables and to identify outliers, incomplete records, or inconsistencies in the data file.

A) Check all study variables by generating descriptive tables

B) Identify problems, correct and clean the file for analysis and hypothesis testing

Overall Description of the Cancer Sample

From our original sample of over 19000 women we created two different sub-samples for analysis. Each sub-sample was selected by going back to the original sample and eliminating the women missing the necessary outcome measure. One sample consists of all the women with available size information and the other of all the women with stage information. The samples did not differ by age, race/ethnicity, or SEER area distribution. Therefore of our original 19008 women, 17009 were in the stage sample and 15967 were in the size sample.

<u>Age</u>

The largest age group in the sample was 70-75 year-olds. They were 30% of the total sample, followed by 75-79 year-olds (26%). Women 85+ were the smallest percentage, only 12%. Women ranged in age from 67 to 106 years old.

When age was dichotomized into two categories for analysis women aged 67-74 years were 44% of the sample and women aged 75 years or older were 56% of the sample.

Race/Ethnicity

The majority of the sample consisted of Caucasian, non-Hispanic women (91%), the remainder was 6% African American and 3% Caucasian Hispanic.

Screening Mammography Use

Overall, 34% of women were non-users of screening mammography. These were women determined to have no screening mammograms in the 24 months prior to diagnosis. The largest group was single users, 51%. These women had one screening mammogram in the 24 months prior to diagnosis. The smallest group was regular users, only 15% of the sample. Regular users had 2 or more screening mammograms.

AJCC Stage at Diagnosis

There were 17009 women with available information on AJCC stage at diagnosis. Almost half of the women were diagnosed with Stage I breast cancer (48%). The next largest group were Stage IIA (22%) and in situ (12%). Women with Stage IIB made up about 8% of the sample. Less than 10% of the sample was diagnosed Stage III or IV.

For most analyses we grouped cancer stage at diagnosis into two groups – local and non-local. Women with in situ or Stage I cancer were considered to be local, which was 60% of the sample. Women with Stage IIA or greater were considered to have non-local cancers. Overall 40% of the women in the sample were diagnosed with non-local cancer.

Size at Diagnosis

There were 15967 women with available tumor size information. For analysis the size variable was treated as continuous 1-110 mm, but for descriptive purposes we categorized it. Most tumors were 1.1-2 cm at diagnosis (37%), followed by those 1cm or less at 31% of the sample, 17% were 2.1 – 3 cm at diagnosis and only 15% were 3.1 cm or greater in size. The mean tumor size in millimeters for the entire sample was 20.3 mm (+/- 17.6mm SD).

Comorbidity

Only 20% of the sample had a comorbidity score greater than 1, which would indicate that they had any sort of inpatient or outpatient treated comorbid condition in the year prior to their breast cancer diagnosis.

Marital Status

Widowed women made up 45% of the sample and married women 40% of the sample. When the variable was dichotomized, more women were not currently married (widowed, separated, single, or divorced) than currently married (59% vs. 41%).

Median Income

Median income was split into two categories - less than 25,000 dollars household income and greater than 25,000 dollars household income. The majority of the sample, 92%, lived in an area with greater than 25,000 dollars median income.

SEER Area

The metropolitan area of Detroit, Michigan contributed the greatest percentage of women to the sample, 16%. Los Angeles, California and the state registries of Connecticut and Iowa each provided approximately 15% of the sample. The smallest percentage of the sample came from the Hawaiian state registry.

Task Three: Conduct analysis of specific aims.

A) To assess the effect of prior mammographic screening on tumor size and stage for women

B) To assess the effectiveness of screening mammography by age group

C) To assess how racial/ethnic differences in the tumor size and stage at diagnosis are affected by previous screening mammography.

Effectiveness of Mammography for Women 67 and Older

In this portion of the project we are interested solely in the effects of prior screening mammography on size and stage of tumor at diagnosis. We begin with a description of how the sample varied by type of mammography user and then look at bivariate associations between different types of use and characteristics such as age and race. This is followed by analysis looking at how prior mammography use affects percent non-local cancer at diagnosis and size of tumor.

Table 2 presents the sociodeomographic characteristics of the sample, stratified by type of prior screening mammography use. The sample corresponds to the women with available stage information, which is a slightly larger group than women with size information (n=17009 vs. 15697).

Regular users are more likely to be in the younger age group (65-74), currently married and living in an area with a higher median income. Whites have the highest number of regular users (15%) while Blacks and Hispanics have the same percentage of women who are regular users (10%). The use of prior screening mammography was significantly different for each characteristic (Table 2).

Table 2. Characteristics of the Sample by Prior Mammography Use[a]

	Non User n=5735	**Single User** n=8757	**Regular User** n=2517
<u>Characteristics</u>	n (%)	n (%)	n (%)
Age*			
67-74	2205 (29)	4049 (53)	1352 (18)
75+	3530 (38)	4708 (50)	1165 (12)
Race/Ethnicity*			
White, non-Hispanic	5121 (33)	7993 (52)	2365 (15)
African American	404 (40)	503 (50)	101 (10)
White Hispanic	210 (40)	261 (50)	51 (10)
Marital Status*†			
Yes, married	2002 (29)	3588 (53)	1250 (18)
No, not currently married	3600 (37)	4955 (51)	1217 (12)
Median Income of Area†*			
Less than $25,000	520 (40)	669 (51)	118 (9)
$25,000 or more	4963 (33)	7740 (52)	2298 (15)

Comorbidity Score*			
Hazard 1 or less	4493 (33)	7083 (52)	2094 (15)
Hazard greater than 1	1242 (37)	1674 (50)	423 (13)

[a] Row Percents
* Likelihood Ratio Chi-Square = p<0.0001
†Marital Status missing 397 observations and Median Income missing 700

Analysis of stage by prior mammography use found that 53% of the nonusers had non-local stage disease (stage II or higher), while only 35% of single mammography users and 26% of regular mammography users had non-local stage cancer. Comparing single users to nonusers, single users have only half the risk of non-local stage disease than nonusers (OR=0.480, 95% CI 0.284-0.349). Regular users have even less risk of non-local stage disease (OR=0.314, 95% CI 0.284-0.349). After adjusting for race, age, comorbidity, SEER area of residence, median income and marital status the odds ratios were approximately the same. The Wald chi-square test was used to determine if the percentage of women diagnosed with late stage disease was significantly different by type of mammography user group. The effect of mammography had a chi-square of 674.39 with a p<0.001, results were similar after adjusting. The percentage diagnosed at late stage disease was significantly different among groups of mammography users.

The overall effect of mammography on tumor size is very strong (unadjuted, F = 453.39, p<0.0001, adjusted F = 369.81, p<0.0001). Table 3 presents the mean tumor size and standard deviation for each group of mammography users.

Table 3. Mean size of tumor stratified by type of mammography user

Mammography Use	n	Mean Size	Standard Deviation
Non-User	5419	25.8 mm	+/- 21.6 mm
Single User	8207	18.2 mm	+/- 14.7 mm
Regular User	2341	15.1 mm	+/- 13.0 mm

Effectiveness of Screening Mammography in Women Aged 75 and Older Compared to Women Aged 67-74

Table 4 presents the characteristics of 17009 women aged 67 and older, diagnosed with breast cancer in 1994 through 1996, stratified by age. Women aged 75 and older were more likely to be diagnosed at a more advanced stage than were women aged 67-74. For example 42% of women aged 75 or greater at diagnosis were diagnosed at stage II or greater compared to 36% of women aged 67-74. Women aged 75 and older were also significantly less likely to be regular users of mammography; that is, women who had at least 2 screening mammograms at least 10 months apart in the 24 months prior to diagnosis. There was also a higher percentage of older women who had no screening mammograms in the 2 years prior to diagnosis. Older women were also significantly more likely to not be currently married or have a comorbidity score greater than one. The two age groups also differed significantly by race/ethnicity and SEER area.

Table 4. Characteristics of 17009 older women with breast cancer diagnosed between 1994-1996 and living in one of the SEER areas by Age at Diagnosis, Column percents

	67-74[a]		75 or older		Totals	
	n=7606		n=9403		N=17009	
Characteristics	n	(%)	n	(%)	N	(%)
Race/Ethnicity*						
White, non-Hispanic	6850	(90)	8629	(92)	15479	(91)
African American	481	(6)	527	(5)	1008	(6)
White Hispanic	275	(4)	247	(3)	522	(3)
AJCC Stage at Diagnosis*						
In Situ	1100	(14)	942	(10)	2042	(12)
Stage I	3742	(49)	4466	(47)	8208	(48)
Stage IIA	1541	(20)	2194	(23)	3735	(22)
Stage IIB	571	(8)	807	(9)	1378	(8)
Stage II, NOS	59	(1)	70	(1)	129	(1)
Stage III A	196	(3)	270	(3)	466	(3)
Stage III B	164	(2)	332	(4)	496	(3)
Stage IV	233	(3)	322	(3)	555	(3)
Median Income of Area[c]						
Less than $25,000	539	(7)	769	(9)	1308	(8)
$25,000 or more	6789	(93)	8212	(91)	15001	(92)
Comorbidity Score*						
1 or less	6368	(84)	7302	(78)	13670	(80)
Greater than 1	1238	(16)	2101	(22)	3339	(20)

SEER area*			
San Francisco	516 (7)	817 (8.5)	1333 (8)
Connecticut	1081 (14)	1476 (16)	2557 (15)
Detroit, Michigan	1356 (18)	1412 (15)	2768 (16)
Hawaii	67 (1)	46 (0.5)	113 (1)
Iowa	997 (13)	1516 (16)	2513 (15)
New Mexico	319 (4)	349 (4)	670 (4)
Seattle – Puget Sound	934 (12)	1074 (11)	2008 (12)
Utah	359 (5)	383 (4)	742 (4)
Atlanta, GA	445 (6)	540 (6)	985 (6)
San Jose, CA	348 (5)	397 (4)	745 (4)
Los Angeles, CA	1184 (15)	1392 (15)	2576 (15)

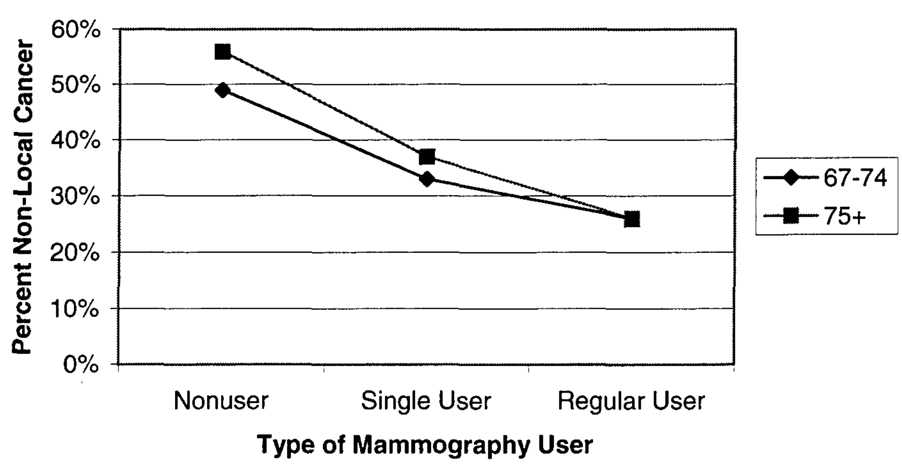
[a]Age started at 67 so that two years of prior Medicare claims data would be available for each woman in the sample.
[b]Mammography Use was defined as 1)non-user – no screening mammograms in the 24 months prior to diagnosis, 2)single user – at least 1 screening mammogram in prior 24 months to diagnosis, and 3)regular user – at least 2 screening mammograms 10 or more months apart
[c]Marital Status information was unknown or missing for 397 women, Data on Median Income was missing for 700
* $p < .0001$

Cancer Stage

Older women (75 years or older) were more likely to present with non-local cancer than the women aged 67-74 (42% vs. 36% (data not shown)) and the size of tumor at diagnosis was larger in older than in younger women (21.5 mm vs. 18.8 mm (data not shown)). This tendency for older women to be diagnosed at later stages led to the next question. Would the effect of prior screening mammography use modify the effect of age on stage and size of tumor at diagnosis? Does regular use of mammography eliminate the previously documented relationship between greater age and increased likelihood of non-local stage disease?

Figure 2 presents the percentage of women diagnosed at non-local stage by age at diagnosis and prior mammography use. Assessing overall differences using logistic regression found that for non-users a greater percentage of women aged 75 and older were diagnosed at non-local stage than women 67-74 (Likelihood Ratio $\chi^2 = 26.97$, $p<0.0001$), the same applied to single users (Likelihood Ratio $\chi^2 = 12.80$, $p=0.0003$). However regular users have the same percentage diagnosed at non-local stage (Likelihood Ratio $\chi^2 = 0.01$, $p=0.9207$). For both age groups nonusers had a higher percentage of women diagnosed at non-local stage than single or regular users.

Figure 2. Percentage of women diagnosed at non-local stage (stage IIA or higher) stratified by type of mammography user and age group (n=17009)



*Nonusers differ from single and regular users for each age group
Regular users have the exact same percentage of non-local cancer for both age groups (26%, p=0.9207)

After looking at the overall trends we were interested in the potential interaction effect of mammography and age on stage of cancer at diagnosis. From before we knew that depending on the age group, likelihood of non-local stage cancer decreased with increased prior use of screening mammography. This interaction of effect of mammography and age had a Likelihood Ratio $\chi^2 = 8.04$ p=0.0180 when unadjusted. When adjusted for other variables such as race, marital status, SES and comorbidity the interaction effect remains significant (Likelihood Ratio $\chi^2 = 8.14$ p=0.0171). Presented in Table 5 is the Analysis of Variation table for the entire model including the interaction effect of age and mammography and all the covariates. It presents the Chi-square values and p-values for each variable in the order it was added to the model.

Table 5. Analysis of Variation for Adjusted Effects of Age and Mammography on Tumor Stage

Source	df	χ^2 Value	P-value
Model	20	771.64	<0.0001
Race	2	32.28	<0.0001
Married	1	69.98	<0.0001
SEER	10	24.95	0.0054
SES	1	9.30	0.0023
Hazard	1	0.59	0.4416
Age	1	41.66	<0.0001
Mammography	2	584.73	<0.0001
Age * Mamm	2	8.14	0.0171
Deviance	15,911	20,643.01	<0.0001

Using contrast statements as part of a cell mean model we were able to quantify the effect of mammography on each age group and found that the effect was greater in the older age group. When nonusers were compared to regular users, the older women have decreased odds of late stage disease (Adjusted OR

0.8556, 95% CI 0.7683-0.9529). Further, regular older users and regular younger users have the same percentage of women diagnosed at non-local stage disease, 26%, and these groups are not statistically different (adjusted analysis p=0.4771). The percentage of non-local stage for single users (33% 67-74 vs. 37% 75+) and nonusers (49% 67-74 vs 56% 75+) are significantly different by age group (adjusted analysis p=0.0021 single, p<0.0001 nonuser).

Tumor Size

Table 6 presents the mean size of tumor stratified by age group and type of mammography use. It also presents mean size adjusted for other predictors of size at diagnosis - race/ethnicity, SEER area, marital status, median income and comorbidity. Non-users and single users had significantly different size of tumor at diagnosis and regular users were not different, similar to stage.

Table 6. Mean size of tumor stratified by type of mammography user and age group – both adjusted and non-adjusted (n=15967)

Screening Mammography Use	Mean Size in Millimeters		Adjusted* Mean Size in Millimeters	
	67-74	75+	67-74	75+
Non-User†	23.9	27.0	25.5	28.3
Single User++	17.3	18.9	19.2	20.6
Regular User§	15.1	15.1	17.1	16.9

*Adjusted for race/ethnicity, SEER area, marital status, median income and comorbidity, n=14970 due to missing values.
† Nonusers young vs. Nonusers old – p <0.0001
++ Single users young vs. Single users old – p <0.0001, p=0.0008*
§ Regular users young vs. Regular users old – p=0.9367, p=0.7728*

We then used analysis of variance to further examine the effects of age and mammography on tumor size. Specifically we were interested in the existence of an interaction effect of mammography and age on tumor size. In the adjusted model the effect of screening mammography on tumor size depended on age (F test 6.03, p<0.0024). This model is presented in Table 7.

Table 7. Analysis of Variance Table for Adjusted Effects of Age and Mammography on Tumor Size

Source	df	Seq SS	Mean Square	F Value	P-value
Model	20	298,335	14,916	51.9	<0.0001
Race	2	22,257	11,129	38.7	<0.0001
Married	1	30,566	30,566	106.3	<0.0001
SEER	10	6,974	697	2.4	0.0070
SES	1	4,506	4,506	15.7	<0.0001
Hazard	1	248	248	0.9	0.3527
Age	1	17,577	17,577	61.2	<0.0001
Mammography	2	212,739	106,369	370.1	<0.0001
Age * Mamm	2	3,468	1,734	6.0	0.0024
Error	14,949	4,296,876	287		
Corrected Total	14,969	4,595,211			

After further analysis using contrast statements we found the effect of prior screening mammography is stronger in older women. Both older single mammography users and older regular mammography users had significantly smaller tumors compared to older nonusers than younger single and regular mammography users comparing to nonusers (single p=0.0118, regular p=0.0003). The size of tumor in regular users is the same for older and younger women (15.1mm) and this is not significantly different (p=0.9367). However single users and nonusers are significantly different depending on age group (p<0.0001).

Effectiveness of Screening Mammography in Non-Hispanic Whites, African Americans and Hispanics

Table 8 presents the sample of 17009 women aged 67 and older diagnosed with primary breast cancer in 1994-96, stratified by racial/ethnic category. African American women were the most likely to be diagnosed with non-local cancer (48%), followed by Hispanic women (45%) and then non-Hispanic white women (39%). White women were more likely to be regular users of mammography, to be currently married, and to live in an area with a median income of greater than 25,000 dollars. Hispanic women tended to be younger than whites and blacks. African American women have a slightly higher percentage of women with comorbidity and were least likely to be currently married. All characteristics were significantly different when tested by Likelihood ratio chi-square ($p<0.0001$).

Table 8. Characteristics of the Study Sample by Race/Ethnicity, Column percents

Characteristics	White n=15479 n (%)	Black n=1008 n (%)	Hispanic n=522 n (%)	Total n=17009 n (%)
Age[a]*				
67-74	6850 (44)	481 (48)	275 (53)	7606 (45)
75+	8629 (56)	527 (52)	247 (47)	9403 (55)
Stage at Diagnosis				
Non-Local	6040 (39)	485 (48)	234 (45)	6759 (40)
Local	9439 (61)	523 (52)	288 (55)	10250(60)
Screening Mammography[b]*				

Nonuser	5121 (33)	404 (40)	210 (40)	5735 (34)
Single user	7993 (52)	503 (50)	261 (50)	8757 (51)
Regular user	2365 (15)	101 (10)	51 (10)	2517 (15)
Marital Status[c*]				
Yes, married	6437 (43)	237 (24)	166 (33)	6840 (41)
No, not currently married	8700 (57)	731 (76)	341 (67)	9772 (59)
Median Income of Area[c*]				
Less than $25,000	859 (6)	363 (37)	85 (18)	1308 (8)
$25,000 or more	13988 (94)	610 (63)	403 (82)	15001 92)
Comorbidity Score*				
1 or less	12514 (81)	743 (74)	413 (79)	13670(80)
Greater than 1	2965 (19)	265 (26)	109 (21)	3339 (20)
SEER area*				
San Francisco	1153 (7)	114 (11)	66 (13)	1333 (8)
Connecticut	2466 (16)	86 (8)	26 (5)	2557 (15)
Detroit, Michigan	2355 (15)	407 (40)	6 (1)	2768 (16)
Hawaii	111 (1)	2 (0.5)	0 (0)	114 (1)
Iowa	2487 (16)	15 (1.5)	11 (2)	2513 (15)
New Mexico	549 (4)	3 (0.5)	117 (22)	671 (4)
Seattle – Puget Sound	1980 (13)	17 (2)	11 (2)	2008 (12)
Utah	727 (5)	5 (0.5)	10 (2)	743 (4)
Atlanta, GA	811 (5)	172 (17)	2 (1)	986 (6)
San Jose, CA	692 (4)	10 (1)	43 (8)	746 (4)
Los Angeles, CA	2168 (14)	178 (18)	230 (44)	2576 (15)

[a]Age started at 67 so that two years of prior Medicare claims data would be available for each woman in the sample.
[b]Mammography Use was defined as 1)non-user – no screening mammograms in the 24 months prior to diagnosis, 2)single user – at least 1 screening mammogram in prior 24 months to diagnosis, and 3)regular user – at least 2 screening mammograms 10 or more months apart
[c]Marital Status information was unknown or missing for 397 women, Data on Median Income was missing for 700
* Likelihood ratio chi-square p < .0001

Cancer Stage

A larger percentage of Hispanic and African American women were diagnosed at non-local stage than non-Hispanic white women (Table 8). Average size of tumor was largest for African American women (25.3 mm) than for Hispanic women (22.3 mm) or white women (19.9 mm). Of interest is whether prior use of mammography mediates the relationship between minority race/ethnicity and later stage cancer at diagnosis. Figure 3 presents the percentage of women diagnosed with non-local cancer stratified by type of mammography user and race/ethnicity.

Figure 3. Percentage of women diagnosed as non-local (stage IIA or higher) stratified by type of mammography user and race/ethnicity

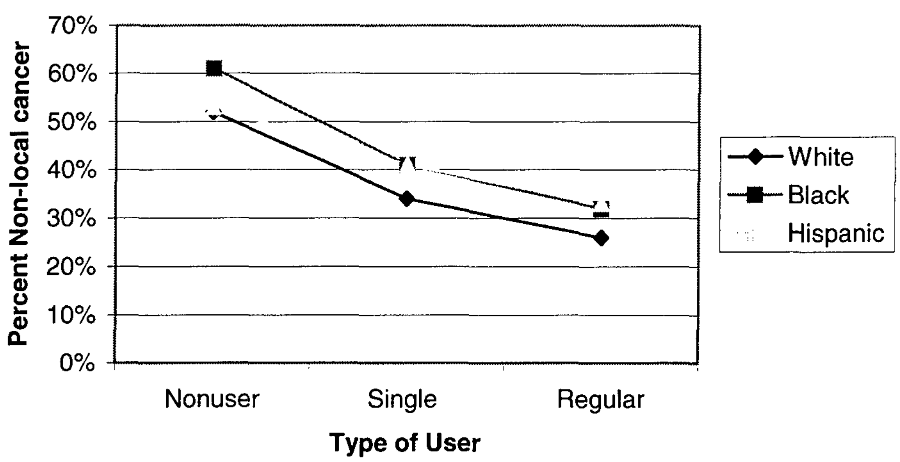


Table 9 presents the analysis of variation table for the final model. At first when all the variables were entered into the analysis of variation model to examine the effect of race/ethnicity and mammography on tumor stage, we tested an interaction of race/ethnicity and mammography. However the interaction of racial/ethnic group and screening mammography was not significant, after adjusting for age, marital status, comorbidity, SEER area and median income (Likelihood Ratio χ^2 = 3.75 p=0.4413). Therefore it was removed from the final model. The overall effect of mammography was significant (Likelihood Ratio χ^2 =584.73, p<0.0001). As was the overall race/ethnicity effect (Likelihood Ratio χ^2 =17.75, p=0.0001).

Table 9. Analysis of Variation for Adjusted Effects of Race and Mammography on Tumor Stage

Source	df	χ^2 Value	P-value
Model	18	763.50	<0.0001
Age	1	68.37	<0.0001
SEER	10	23.54	0.0089
SES	1	21.88	<0.0001
Hazard	1	1.01	0.3139
Married	1	46.23	<0.0001
Race	2	17.75	0.0001
Mammography	2	584.73	<0.0001
Deviance	15,913	20,651.14	<0.0001
Race * Mamm*	4	3.75	0.4413

*Not included in final model

Further, white women who were regular users of mammography were diagnosed with non-local cancer 26% of the time, black women 32% of the time, and Hispanic women 33% of the time and statistically these percentages were not different (Likelihood Ratio χ^2 =3.07, p=0.2158).

Tumor Size

Based on women in the sample with available information on tumor size (n=15697), size of tumor does vary by ethnicity. White women's tumors were on average 19.9 mm in diameter with a standard deviation of 17.3mm, and the smallest of all three groups. Hispanic women had tumors averaging 25.3mm (SD +/-17.8mm) and African American women's tumors were an average of 25.3mm (SD +/- 21.4mm). Table 10 presents the mean size of tumor stratified by race/ethnicity and category of prior screening mammography use. It also presents the mean size of tumor adjusted for other common predictors of size including age and comorbidity.

Table 10. Mean Size of Tumor stratified by type of mammography user and racial/ethnic group – both Adjusted and Non-Adjusted (n=15967)

Mammography Use	**Mean Size of Tumor in Millimeters**		
	Non-Hispanic White	African American	Hispanic White
Nonuser†	25.3	31.6	27.1
Single User++	17.9	21.7	19.5
Regular User§	14.9	17.7	16.7
Mammography Use	**Adjusted Mean Size of Tumor in Millimeters***		
	Non-Hispanic White	African American	Hispanic White
Nonuser†	25.6	30.6	25.6
Single User++	18.5	21.4	20.1
Regular User§	15.7	18.1	16.2

* Adjusted for age, SEER area, marital status, median income and comorbidity based on 14970 usable observations.
† Nonusers white vs. Nonusers black vs. Nonusers Hispanic – $p < 0.0001$, adjusted $p < 0.0001$
++ Single users white vs. Single users black vs. Single users Hispanic – $p < 0.0001$, adjusted $p = 0.0028$
§ Regular users white vs. Regular users Black vs. Regular user Hispanic – $p = 0.2404$, adjusted $p = 0.4443$

We then used analysis of variance to further examine the effects of race/ethnicity and mammography on tumor size. Again we were interested in the existence of an interaction effect of mammography and race/ethnicity on tumor size. However in the model the effect of screening mammography on tumor size did not depend on race/ethnicity and was then dropped from the final model (F test 1.1, p=0.3656). This final model is presented in Table 11.

The effect of mammography on size was significant (F = 369.8, p<0.0001). As was the effect of race on size (F = 22.9, p<0.0001).

Table 11. Analysis of Variance Table for Adjusted Effects of Age and Mammography on Tumor Size

Source	df	Seq SS	Mean Square	F Value	P-value
Model	18	294,867	16,382	57.0	<0.0001
Age	1	29,277	29,277	101.8	<0.0001
Married	1	23,474	23,474	81.6	<0.0001
SEER	10	5,703	570	2.0	0.0310
SES	1	10,224	10,224	35.6	<0.0001
Hazard	1	253	253	0.9	0.3481
Race	2	13,196	6,598	22.9	<0.0001
Mammography	2	212,739	106,369	369.8	<0.0001
Error	14,951	4,300,344	288		
Race * Mamm	4	1,240	310	1.1	0.3656
Remaining Error	14,947	4,299,104	288		
Corrected Total	14,969	4,595,211			

Summary of Findings

What can we conclude from the analyses? First, that use of prior screening mammography had a significant effect on cancer size and stage at diagnosis. Women receiving even a single screening mammogram prior to diagnosis had improved size and stage at diagnosis, and women with prior regular screening mammography use had the greatest benefit.

After observing the previously seen differential whereby older women are diagnosed at later stages and with larger tumors, we investigated if use of screening mammography modified this relationship. Mammography did interact with age in such a way that there was greater affect in the older women (75 and older) even controlling for other factors such as race and comorbidity. Older and younger regular users of mammography prior to adjusting with covariates end up having the exact same size of tumor and percentage diagnosed at non-local stage.

Finally, after investigating the relationship between race/ethnicity, mammography use and size/stage at diagnosis we found that while mammography alone has a significant effect on mammography there is no significant interaction between race and mammography. However among regular users of mammography African Americans, Hispanics, and whites are not significantly different in size or stage at diagnosis.

Unfortunately the quality of the socioeconomic data prevented us from conducting any detailed analysis of the effect of income on size and stage and diagnosis and use of screening mammography. A crude measure of socioeconomic status was used in the model as a control variable.

Key Research Accomplishments:

- Investigation of the relationship between prior screening mammography use and cancer stage and tumor size at diagnosis for women aged 67 and older diagnosed with primary breast cancer in 1994, 1995 or 1996
- Found that use of screening mammography was associated with reduced tumor size and lower stage in women 67 and older
- The relationship between older age and later stage cancer / larger tumor size was eliminated by regular mammography use (2 mammograms at least 10 months apart in the two years prior to diagnosis) in women aged 75 and older compared to women aged 67-74.
- The relationship between minority race/ethnicity and later stage cancer/ larger tumor size was modified by regular mammography use, but it did not completely eliminate differentials

Reportable Outcomes:

Manuscript

Randolph WM, Goodwin JS, Mahnken JD, Freeman JL. Outcomes of Screening Mammography in Women Aged 75 and Older: Regular use of mammography eliminates age-related disparities in size and stage of breast cancer at diagnosis. Submitted to the Annals of Internal Medicine – June 2001

Dissertation

Randolph WM. *Effectiveness of Screening Mammography in Women from Older and Disadvantaged Populations.* Copyright 2001.

Degrees

Doctor of Philosophy Degree Received May 12^{th}, 2001

Post-Doctoral Fellowship Applications

Epidemic Intelligence Service, Centers for Disease Control and Prevention, Applied August 2001, Interview October 2000, Withdrew Application December 2000.

Cancer Research Training Award from the National Cancer Institute's Cancer Prevention Fellowship Program, Applied September 2001, Interview November 2000, Offered Position November 30, 2000, Accepted December 2000.

Conclusions:

In summary we found that screening mammography was associated with reduced tumor size and lower cancer stage in women 67 and older. This supports the recommendation that women older than age 70 continue to receive annual mammography.

A major factor contributing to the poor survival experience of older women with breast cancer, relative to younger women, is delay in diagnosis of cancer. Our results suggest that the more advanced stage and larger size of breast cancer at diagnosis seen in older women is completely eliminated in women who undergo regular mammography. Regular mammography use has a greater effect, in terms of reducing size and stage of tumor at diagnosis, in women age 75 and older than in women 67 to 75. These results provide strong evidence for recommending yearly mammography screening in women aged 75 and older.

While there was no interaction of race/ethnicity and mammography there was a strong effect of mammography on all three groups which eliminated significant differences among regular users of mammography. Our lack of significant finding concerning an interaction of race and mammography may be due to the small sample size of both minority groups.

Strengths and Limitations

The results of this study should be interpreted with an understanding of the limitations of its methodology. The major limitation is that, in observational studies, it is impossible to conclude that the association of regular mammography use and lower stage and size of breast cancer at diagnosis is causal. It is probable that the cohort of women who undergo regular mammography are also more likely to receive regular medical care and be more health conscious in general, which could have contributed to the smaller size and earlier stage at diagnosis of breast cancer. Another limitation is the exclusion of older women enrolled in Medicare HMOs, because of incomplete information from Medicare charges from that group.

An important limitation in our ability to conclude anything about effectiveness in Hispanics and African Americans compared to non-Hispanic whites was the small sample size of both minority groups. The difference between the groups did not disappear with regular use of mammography which could potentially be due to biological factors, access to health care or reduced health care follow-up for minorities. It is also possible that our Hispanic group was small due to lack of insurance coverage through Medicare because they were ineligible for coverage.

There were many strengths of the study. First of all was the large overall sample size. There were more than 17,000 older women in the sample diagnosed with breast cancer in the years 1994, 1995 and 1996 who had information on previous mammography use. The study used high quality data from the SEER program. One of the reasons this added to the study was that he population covered by the SEER registry represents approximately 14% of the United States, with good representation from all geographic areas and ethnicities, which supports the generalizability of the findings to the remainder of the US population. The study not only used cancer stage at diagnosis as an outcome which is often used as an indicator but also utilized tumor size which may be a better indicator of the effectiveness of mammography.

Another important strength of study was the use of the screening mammogram algorithm to assess prior screening mammography use. Because we used an algorithm to examine each mammogram a woman had we were both able to include screening mammograms miscoded as diagnostic but exclude diagnostic mammograms miscoded as screening. Finally our study was only one of a few studies of mammography to include women over the age of 75 years. Because of this we were able to gather important information about how mammography works in this older age group.

Research Implications and Future Directions

There are implications for screening recommendations in older women. First of all there are no consistent recommendations for older women. One of the problems with recommending mammography to older women has been the lack of data on its efficacy in women ages 74 and older. Only a few studies have included women over 70 and no clinical trials have reported results for women over age 74 (Fletcher SW et al. 1993, Kerlikowske et al. 1995, US Preventive Services, Tabar L et al. 1995, Chen et al. 1995). Here we are showing that the effectiveness of mammography is the same in women over 75 to that in women 67 to 74. Other studies have also demonstrated the effectiveness of screening mammography in older women. Our data gives strong support for routine screening.

African American and Hispanic women were significantly more likely to be diagnosed with non-local stage disease and larger tumors than white women. However when women were regular users of mammography the difference was not significant. Mammography alone has a substantial effect but it does not interact with race/ethnicity. Regular use of screening mammography eliminates much of the negative effect of age and race/ethnicity on size and stage of tumor at diagnosis.

This study both improved on and replicated parts of previous studies that have used linked data to study mammography use in older women. More importantly, it utilized data from years after Medicare began paying for mammographic screens and after the implementation of the Mammography Quality Standards Act. In contrast to other studies, this project included data from all SEER areas so that more in-depth research into racial and ethnic differences could be conducted. In addition, it focused on the differences in breast cancer by age, and provided useful information about the rapidly growing population of the oldest-old, a population that has not been included in the clinical trials of mammography.

This research added to our knowledge about the effectiveness of mammography in community practice by exploring age and racial/ethnic differences in mammography use, and how they affect differences in breast cancer stage at diagnosis. It is relevant to the fight against breast cancer in that if mammography is just as effective in older and disadvantaged women, then we can promote mammography to these older women as a method of early cancer detection. If it is found to not be as effective in older women, older minority women, or women with lower socioeconomic status, then we must further explore the potential reasons for this decreased effectiveness since these older women bear a significant level of morbidity and mortality from breast cancer. While there is no efficacy data regarding mammography in this age group, there is effectiveness data demonstrating benefit to older women.

The foundations of evidence-based medicine rest on information from randomized controlled trials. Unfortunately, no trial has reported results of mammography in women over age 74, and it is unlikely that such a trial in older women will be undertaken in the future. This lack of data on efficacy of mammography in older women has resulted in uncertainty among clinicians and inconsistency among different mammography guidelines produced by professional organizations and consensus panels (US Preventive Services Task Force 1996, AGS Clinical Practice Committee 1999). Still there is the question of when routine screening for women should be stopped. Unfortunately this is a complex question may not be answerable only by assigning an age to stop screening, other factors such as comorbidity and life expectancy may need to be taken into account. One must also keep in mind that false positives may cause significant comorbidity in women older than age 70 (Welch and Fisher 1998).

In summary we reiterate that older women may be less likely to use routine screening mammography due to conflicting recommendations and lack of endorsement by their physician. Physicians need to be aware that the life expectancy of older women is much longer now; for example, women 75 years of age can expect to live 12.1 years longer and therefore there is more time for them to benefit from early detection of breast cancer. While there is limited clinical trial data for women over 70 and experts disagree whether to recommend mammography for women 75 and older, this study shows that regular and even single use of mammography reduces tumor size and stage at diagnosis. The data suggest that increased stage of cancer and size of tumor in older women is related to mammography use and could be eliminated by increasing mammography use in this group of older women.

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DEPARTMENT OF THE ARMY
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 28 Aug 02

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Phylis M. Rinehart

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
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